Licensing and Translational Issues with Personalized Medicine

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March 2, 2007
Highlight Issues From the Front Lines

• Real life example of personalized medicine

• Two licensing challenges

• Translational challenges
Personalized Medicine

*Genomics today is where the computer industry was in the 1970s -- at the beginning of a technology revolution...*

Biotechnology + Bioinformatics + Genomics

= Revolution in Healthcare
Risk prediction

- Begin colonoscopy at age 40
- Avoid high fat in diet

Pharmacogenomics

- Drug dose of antidepressant determined by drug metabolism genetic profile

New Therapies

- Gene-based drug therapy for cancer
- Gene therapy for heart disease
Example of What a Genomics Medicine Center Can Bring our Patients - “Target Now”

Patient calling Nurse Turner:

“I am calling from New Jersey and have a rare tumor for which there is no treatment – I need some help”

What can I do?

Judy Turner, R.N.
More Details on the Patient

1. 63 year old woman with adenoid cystic carcinoma of the breast
   - extensive lung metastases (now symptomatic)
   - prior therapy with
     • 5FU
     • vincristine
     • cytoxan
     • methotrexate
     • thalidomide
     • phase I farnesyl transferase inhibitor
4. The patient’s tumor was sent to us and was processed for microarray – 30,000 gene chip to perhaps aid in selection of a new agent – also processed for immunohistochemistry.
<table>
<thead>
<tr>
<th>Ratio T/Ref</th>
<th>Gene Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.862</td>
<td>TXNIP</td>
<td>Thioredoxin interacting protein (vitamin D-3 upregulated protein-1), a negative regulator of thioredoxin that is induced by the stress response and may play a role in the redox regulation of differentiation, may have an anti-tumor effect</td>
</tr>
<tr>
<td>6.857</td>
<td>I_1002429</td>
<td>Protein containing 11 leucine rich repeats, and a leucine rich repeat N-terminal cysteine rich domain, has weak similarity to thyroid stimulating hormone receptor (human TSHR), which is a G protein-coupled receptor that regulates thyroid cells</td>
</tr>
<tr>
<td>6.848</td>
<td>EPHB4</td>
<td>Ephrin type B receptor 4, a member of the Eph-related subfamily of receptor tyrosine kinases, preferentially enhances megakaryocytic and erythrocytic differentiation of progenitor cells; expression is elevated in colon carcinoma</td>
</tr>
<tr>
<td>6.826</td>
<td>CLSP</td>
<td>Calmodulin-like skin protein, a member of the calmodulin family of calcium-binding proteins, may play a role in keratinocyte differentiation, shows altered expression in sun-damaged skin</td>
</tr>
<tr>
<td>6.767</td>
<td>I_965438</td>
<td>Retired, was Protein with high similarity to immunoglobulin lambda (mouse 1810027001Rik), which associates with heavy chains to form antibodies (immunoglobulins), contains two immunoglobulin (Ig) domains</td>
</tr>
<tr>
<td>6.717</td>
<td>NM_003425.1</td>
<td>Homo sapiens zinc finger protein 45 (a Kruppel-associated box (KRAB) domain polypeptide) (ZNF45), mRNA</td>
</tr>
<tr>
<td>6.648</td>
<td>LIPH</td>
<td>Lipase member H, phospholipase that may be involved in lipid metabolism, a member of the triglyceride lipase family, contains an amino-terminal lipase domain and a carboxy-terminal domain</td>
</tr>
<tr>
<td>6.600</td>
<td>CBX7</td>
<td>Protein containing a Chromo domain, which bind chromatin, has moderate similarity to a region of chromobox homolog 4 Drosophila Pc class (human CBX4), which is a component of the HPC-HPH Polycomb group complex and functions as a transcriptional repressor</td>
</tr>
<tr>
<td>6.567</td>
<td>FLJ21511</td>
<td>Protein with low similarity to S. cerevisiae Cwh43p, which is involved in maintenance of cell wall integrity</td>
</tr>
</tbody>
</table>

An easy target identified – vitamin D receptor. Patient placed on calcitriol (note DN 101) no change in tumor from January 2004 - January 2005
The Patient Decided to be Followed at The Virginia G. Piper Cancer Center

Was doing well on vitamin D until January 2005. Unfortunately she then had increasing disease and bone mets with bone pain

• Also had very bothersome cough
Second Target Noted on Microarray and by IHC

Other target present was
- PDGFR (Platelet derived growth factor receptor)
- Inhibitor molecules
  - Gleevec
  - SU11248
  - BAY43-9006

Microarray done to look for possible target(s)

Patient began on Gleevec February 14th, 2005 – bone pain disappeared! Looked and felt great.
Clinical Trial Schema

Patient with advanced refractory cancer, progression on at least two previous treatment regimens

After informed consent, biopsy tumor

Microarray and IHC analysis

Target Found?

YES

Treatment based on target found

Follow-up every eight weeks

NO

Treatment based on empirical basis

Follow-up every eight weeks

Primary Endpoint: Time patient is on therapy (compared to time patient was on therapy on which their tumor had just progressed.)
Inclusion Criteria

1. Informed consent and ≥ 18 years of age
2. Life expectancy > 3 months
3. Have metastatic cancer which has documented progression on 2-3 prior regimens for advanced disease
4. Patients with solid tumors measurable or evaluable (PSA ok for patients with prostate cancer)
5. KPS ≥ 80% (ECOG 0-1)
6. Good medical candidate for and willing to undergo a biopsy or surgical procedure to obtain tissue
7. Bone Marrow – WBC ≥ 3000, ANC ≥ 1,500; Hgb >9; plt > 100,000
8. Renal: creat. ≤ 1.5 mg/dl
9. Hepatic Bili ≤ 1.5 x ULN; Usual SGOT/SGPT; Albumin ≥ 3.5 g/dl
Number of Patients

1. 92 patients*
   - 64 treated based on molecular profiling
   - Up to 28 no molecular target found – treat with a phase I agent
2. Planned start
   - July 2006
3. Planned closure
   - January 2008

*Note: There will be two of these
An Example of a Licensing Challenge

• Accurately defining the field of use.
  ✓ Molecular Diagnostics?
  ✓ Pharmacogenomics?
  ✓ Gene profiling?
  ✓ Molecular profiling?
  ✓ Biomarkers?
Licensable Technology
Deal #1
Deal #3

Can you do a deal #4?
Valuations

More Art than Science

- Market Comparisons
- Replacement Cost (Savings)
- Future cash flows
Translational Challenges

• Validation
  - Peer review
  - Clinical trials

How valid is the validation?
Translational challenges - cont

• Sample accrual
  - Those are my samples!

• How do you share data and still maintain a barrier to entry from competitors?
  - Novartis - type 2 diabetes data to be released to the public?
Novartis, The Broad Institute, and Lund University announce release of genome-wide analysis of genes associated with type 2 diabetes and related metabolic disorders

“To translate this study's provocative identification of diabetes-related genes into the invention of new medicines will require a global effort. We hope many will race to do so," said Mark Fishman, President of the Novartis Institutes for BioMedical Research. "We hope as well that others adopt this novel and effective mode of open collaboration between scientists and physicians, in business and academia, and dedicate work to our patients by making the data quickly and freely available to all.”

Media releases, Novartis.com
February 12, 2007
Translational Challenges

- Funding projects that are post discovery and pre-development.
Bridging the Financing Gap in Drug Development

Traditional Philanthropy/Government

Target/Lead Discovery & Validation

Pre-Clinical Development

Clinical Development

Approval and Marketing

Venture Capital

Big Pharma

Private Equity/Public Markets

FINANCING GAP

Risk

Low

Translational Genomics Research Institute
Earlier Diagnoses, Smarter Treatments
## Recent Biotech Activity

### Recent Biotech Activity Of Representative Disease-Focused Foundations

<table>
<thead>
<tr>
<th>Foundation</th>
<th>Total money provided in support of R&amp;D to date</th>
<th>Biotech company projects/grants (date)</th>
<th>Focus of project</th>
</tr>
</thead>
<tbody>
<tr>
<td>The ALS Association</td>
<td>$30M</td>
<td>Galapagos (BioFocus DPI) and Stem Cell Innovations may receive up to $3M over 2 years (12/06)</td>
<td>Screening of adeno viral siRNA collection in human motor neurons to identify drug targets for new therapies for amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>CHDI and the High Q Foundation</td>
<td>ND</td>
<td>MethylGene and collaborator EnVivo Pharmaceuticals awarded up to $1.5M in initial funding (11/06)</td>
<td>To fund the development of histone deacetylase inhibitors as drugs for Huntington disease</td>
</tr>
<tr>
<td>European Crohn’s and Colitis...</td>
<td>ND</td>
<td>PDL BioPharma (10/06)</td>
<td>Collaboration to support global clinical trials of visilizumab for severe IV steroid refractory ulcerative colitis</td>
</tr>
<tr>
<td>Juvenile Diabetes Research...</td>
<td>$1B</td>
<td>Sangamo BioSciences will receive up to $3M in funding (10/06)</td>
<td>To support Phase II trials of SB-509 for treating diabetic neuropathy</td>
</tr>
<tr>
<td>Leukemia &amp; Lymphoma Society</td>
<td>$483M</td>
<td>Ensemble Discovery (11/06)</td>
<td>Development of assay to detect cells responsible for resistance to initial therapy for CML</td>
</tr>
<tr>
<td>Multiple Myeloma Research...</td>
<td>$70M</td>
<td>Semafore Pharmaceuticals and ProChon Biotech each awarded $1M grant (12/06)</td>
<td>To fund the development of lead compounds through early-stage clinical trials</td>
</tr>
<tr>
<td>Company</td>
<td>Investment Model</td>
<td>Committed Capital ($M)</td>
<td>Amount Invested ($M)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Symphony Capital</td>
<td>Fund buys IP rights to compounds from a biotech or pharma company and develops compound in clinic. Company has option to buy back IP at set price and time.</td>
<td>$315</td>
<td>$136</td>
</tr>
<tr>
<td>TPG-Axon Capital</td>
<td>Uses some of the firm’s $6 billion to finance product development. No transfer of IP but provides cash, services, and sales force to help development. Royalties, milestones.</td>
<td>&gt;$1,000</td>
<td>&lt;$500</td>
</tr>
<tr>
<td>NovaQuest (formerly Pharmacia Development Group, a subsidiary of Quintiles Transnational)</td>
<td>No transfer of IP. NovaQuest puts up cash and services in return for milestone and royalties.</td>
<td>$1,500</td>
<td>$750</td>
</tr>
<tr>
<td>Celtic Pharma</td>
<td>Buys IP rights to products that are in the clinic from companies. No predetermined buy-back provision. Auctioes the compound after clinical trials completed.</td>
<td>$250</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>Royalty Pharma</td>
<td>Pays upfront for long-term royalty streams of products that are on the market or still in the clinic.</td>
<td>$140</td>
<td>$90</td>
</tr>
</tbody>
</table>
Summary

• The rapidly evolving field of Personalized Medicine has presented some licensing challenges in the areas scope and value. The effects of current license terms are yet to be realized.

• Sample accrual, validation, data integration, and financing present significant challenges for effective translation.

• Market forces are finding ways to mitigate the challenges.